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C-reactive protein and 10-year cardiovascular risk in rheumatoid arthritis

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ABSTRACT

Objectives: To evaluate the association between C-reactive protein (CRP) and 10-year risk of cardiovascular (CV) events using the Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis (ERS-RA), based on conventional and RA-specific risk factors but not CRP, in RA patients without previous cardiovascular events. **Methods:** ERS-RA was calculated in 1,251 "Cardiovascular Obesity and Rheumatic Disease Study (CORDIS)" database patients [(age 60.4(9.3) years; 78% female; disease duration, 11.6(8) years; CDAI, 9(9); CRP, 6.8(12) mg/L]. **Results:** The mean (SD) 10-year risk of CV events was 11.6% (0.9). After adjusting for the use of DMARDs and biologics, CRP concentrations were significantly associated with 10-year risk of CV events (coefficient=0.005 for each 10 mg/L CRP increment; 95%CI 0.000-0.111; p=0.047). In mediation analysis, the association between CRP and ERS-RA was not explained by disease activity. **Conclusion:** In a large cohort of RA patients without previous cardiovascular events, a 20 mg/L increase in CRP concentrations was associated with a 1% increase in 10-year risk of CV events. This suggests that actively targeting residual inflammatory risk beyond conventional and RA-specific risk factors might further reduce CV event rates in RA patients.

KEYWORDS

Inflammation; C-reactive protein; myocardial infarction; stroke; cardiovascular risk score.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease compared with the general population[1]. The increased risk of cardiovascular disease in patients with RA is due to the composite effect of genetic predisposition, traditional cardiovascular risk factors, and the presence of chronic oxidative stress[2–4] and systemic pro-inflammatory state. Cardiovascular disease in RA population develops through multiple mechanisms, including accelerated endothelial dysfunction, early arterial stiffening, modifications of central hemodynamics, and premature atherosclerosis[5–7]. As a consequence, RA patients are exposed to increased risk of coronary dysfunction[6], atherosclerotic disease, atrial fibrillation, and arrhythmogenic sudden death[8].

However, a significant reduction in the incidence of cardiovascular events has been reported in recent studies, suggesting a more effective control of disease activity and inflammatory burden secondary to early aggressive treatment in the context of a treat-to-target approach[9,10,11,1213]. Therefore, as proposed in the general population, a better control of residual inflammatory risk may further reduce cardiovascular morbidity and mortality in RA patients.

Among the available algorithms to estimate cardiovascular risk, the Expanded Cardiovascular Risk Prediction Score for RA (ERS-RA) has been specifically developed for the RA population. ERS-RA estimates the 10-year risk of myocardial infarction, stroke or cardiovascular-related death based on conventional and RA-specific (clinical disease activity index-CDAI, disease duration, HAQ, glucocorticoid use) risk factors[14].

C-reactive protein (CRP), a marker of low-grade inflammation, has been linked to cardiovascular risk in RA [15,16]. Classic studies have indicated that CRP is a marker of subclinical atherosclerosis, cardiovascular events and cardiovascular mortality in patients RA[17,18]. However, CRP is not included in the ERS-RA, and there is no information regarding the comparison between CRP and ERS-RA-predicted cardiovascular risk or the possible influence of individual ERS-RA components on the relationship between CRP and ERS-RA.

We sought to address this issue by investigating the association between CRP plasma concentrations and 10-year risk of cardiovascular disease predicted by ERS-RA, and the indirect effect of CRP on individual components on ERS-RA in an established RA cohort without previous cardiovascular events, the "Cardiovascular Obesity and Rheumatic Disease Study (CORDIS)" database[19].

The use of ERS-RA over other cardiovascular risk scores was justified by the fact that we were interested to explore the relationship of CRP both with the predicted 10-year risk score and each RA-specific cardiovascular risk factor included in the score.

PATIENTS AND METHODS

Study design

The CORDIS database[19] collected the following data of RA patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR classification criteria[20]: age, sex, smoking status (current, former, never), body mass index, systolic and diastolic blood pressure, lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), diabetes and hypertension. Hyperlipidemia was defined as the use of lipid-lowering medications and/or low-density lipoprotein (LDL) cholesterol target according to their cardiovascular risk as defined by ESC/EAS Guidelines for the management of dyslipidemias[21]. Hypertension was defined either as a history of hypertension or current use of blood pressure lowering drugs. Diabetes was defined based on previous medical history and/or use of oral hypoglycemic medications or insulin. Disease-specific descriptors included disease duration, Health Assessment Questionnaire (HAQ) disability index as function index, and Clinical Disease Activity Index (CDAI) as measures of disease activity. Serologic status included rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) as determined according to local assays. Finally, ongoing anti-hypertensive and lipid-lowering therapies and anti-rheumatic drugs, including conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), biologic (b) and targeted synthetic (ts) DMARDs and corticosteroids were recorded.

The following data were extracted from the CORDIS database for the calculation of the ERS-RA risk score: 1) conventional cardiovascular risk factors: sex, hypertension, diabetes, hyperlipidemia, current tobacco use, and 2) RA-related cardiovascular risk factors: CDAI, HAQ, prednisone use, and disease duration >10 years.

Participants were then classified into four 10-year predicted cardiovascular risk categories, according to the Adult Treatment Panel III (<5%, >=5 to 10%, >=10 to 20%, and >20%)[22].

Statistical analysis

We conducted a one-way ANOVA to determine differences in mean ln-CRP (CRP logarithm) plasma concentrations across ERS-RA categories. We assessed independent associations between ERS-RA risk score and individual relevant variables using multivariate regression (ENTER approach; listwise deletion analysis). Given the relatively high number of missing CRP data (n=385), regression analysis was also performed using multiple imputation (10 sets). Regression models were not adjusted for independent variables included in the ERS-RA score. We used mediation analysis to assess the direct and indirect effects of ERS-RA components and immunosuppressive drugs on the total ERS-RA score. The mediation analysis was performed using the "sem" structural equation modelling commands in Stata and the direct, indirect and total effects of ERS-RA components and medications were calculated using the "estat effects" post-estimation command. Both ERS-RA and CRP were log-transformed prior to the analysis. Analyses were performed using Stata 16.1 in Stata 16.1 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). A p-value < 0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not directly involved in the design or completion of this study.

RESULTS

Patients' characteristics

As described in Table 1**,** participants (n=1,251) were mostly middle-aged women with low to moderately active long-standing RA [age 60.4(9.3) years; 78% female; disease duration, 11.6(8) years; CDAI, 9(9)]. Mean CRP plasma concentrations were 6.8 mg/L, corresponding to a relatively low level of systemic inflammation.

A total of 539 (43%) patients received glucocorticoids, 676 (54%) a b/tsDMARD, and 885 (70.4%) at least one csDMARD.

According to inclusion criteria, participants had not a history of myocardial infarction, stroke, or coronary revascularization.

ERSRA and hs-CRP

The mean ERS-RA score was 0.12 ± 0.10. There was a statistically significant difference in ln-CRP plasma concentrations across the four ERS-RA categories [$F(3,778)=4.48$, $p=0.004$] (Figure 1). A Bonferroni post-hoc test revealed that ln-CRP plasma concentrations in the third and fourth risk categories were significantly higher than the first (Delta ln-CRP 0.32, p=0.01; Delta ln-CRP 0.30 mg/L, p=0.034, respectively). However, there were no significant differences between ln-CRP plasma concentrations in the third and fourth categories and the second.

After adjusting for the use of csDMARDs and b/tsDMARD, CRP plasma concentrations were significantly associated with the ERS-RA score both in standard multiple regression and in regression with multiple imputation: the adjusted mean increment in the ERS-RA score was 0.005 (0.006 in the regression after multiple imputation) for any 10 mg/L increment in CRP concentrations, p=0.047 (p=0.039 after multiple imputation) (Table 2).

In mediation analysis, none of the individual ERS-RA components or medications had any indirect effects on the total ERS-RA mediated via hs-CRP (Table 3). However, as expected, most individual ERS-RA components had a significant direct effect on the ERS-RA score. The total effects were similar in magnitude to the direct effects (Table 3).

DISCUSSION

We explored for the first time the association between CRP plasma concentrations and 10-year cardiovascular risk predicted by the ERS-RA score in a population of RA patients without previous cardiovascular events.

The predicted ERS-RA score, 0.12 ± 0.10, indicated a moderate 10-year risk of cardiovascular disease; This likely reflects the specific characteristics of the population, mostly represented by middle-aged RA women with high prevalence of hypertension and hyperlipemia, longstanding disease, and frequent use of prednisone.

We found a significant correlation between CRP and 10-year cardiovascular risk predicted by ERS-RA score, with an increase of 1% in cardiovascular risk for every 20 mg/L increase in CRP concentrations.

Our finding of a significant and positive association between CRP and cardiovascular risk is in agreement with mounting evidence of CRP as a proxy of cardiovascular risk factor in the RA population, with higher CRP concentrations being reported to be associated with an increased risk for subclinical atherosclerosis progression and increased incidence of major cardiovascular events[15].

A recent prospective population-based study showed that RA patients free of cardiovascular disease and carotid plaques being in the moderate-high DAS28-CRP disease activity at baseline displayed a higher odds ratio for the appearance of carotid plaque (OR 2.26 [95% CI 1.02-5.00], p = 0.044) after a 5-year follow-up compared to those in the remission category[13].

In a retrospective cohort study (2005–2010 data from a United States commercial health plan, 44,418 eligible RA patients) CRP>10 mg/L compared with <1 mg/L was associated with increased risk of myocardial infarction (HR 2.12; 95% CI 1.02 to 4.38)[23]. Similarly, the risk of cardiovascular death was increased in patients with higher CRP (HR 3.3 [95% CI 1.4?7.6] for CRP >5 mg/L)[24].

Although the coefficient of regression between CRP and ERS-RA-calculated cardiovascular risk in our analysis is relatively low, the association may be clinical meaningful in the context of a high-grade inflammatory state: thus, a CRP plasma concentration of 100 mg/L, corresponding to an increase of 5% of ERS-RA score, may reclassify the cardiovascular risk of a RA patient with high inflammatory disease from the moderate to the moderately-high risk stratum. Similar to our results, an increase of 100 mg/L of plasma CRP concentrations has been reported to be associated with an increased risk of heart failure (HR 1.25, 95% CI 1.06 to 1.48)[25].In our study CRP plasma concentrations were not associated with any individual component of the score, including conventional cardiovascular risk factors. In particular, as resulted from the mediation analysis, the association between CRP and cardiovascular risk score calculated by ERS-RA, was not driven by disease activity. The lack of relationship between CPR and disease activity (expressed as CDAI) in the mediation analysis might be related to the characteristics of our study population, which included RA patients chronically treated with anti-inflammatory drugs, the moderate disease activity (mean CDAI=9) and relatively low mean CRP. Moreover, these findings may suggest the existence of a residual detrimental cardiovascular effect of systemic inflammation beyond this related to the RA disease itself.

Similarly to our results, CRP concentrations have been shown to be significantly correlated with 10-year Framingham Coronary Heart Disease Risk but not with most individual components of this score26. Moreover, in two large prospective epidemiological cohort studies (Physicians' Health Study and Women's Health Study), subjects in the highest quartile of CRP had a significant increase in the risk of major cardiovascular events and this risk was largely independent from conventional cardiovascular risk factors[27,28].

Collectively taken, these data suggest that the assessment of CRP may provide information that complements, rather than duplicates, that captured by conventional risk factors. Despite the low coefficient of association between CRP and cardiovascular risk, our results still are significance, as they suggest that a substantial number of RA patients with well-controlled disease may experience cardiovascular events due to residual inflammatory risk. These data support the hypothesis that aggressive treatment of inflammatory burden, in the context of a comprehensive disease control, may curtail the incidence of cardiovascular events in RA patients.

Accordingly, in interventional trials, targeting residual inflammatory risk has proven to reduce the rate of cardiovascular events in the general population[12,29].

This work has some potential limitations.

First, due to the study's cross-sectional nature, a cause-effect relationship between CRP concentrations and increased cardiovascular risk as predicted by ERS-RA cannot be firmly established. Second, most of RA patients included in the CORDIS database were under immunosuppressive and anti-inflammatory therapy at enrollment, which may have mitigated the strength of the association between CRP and ERS-RA score[30–33]. In particular, in the current study, a large proportion of patients were exposed to glucocorticoids (43%) at the moment of the analysis and during the disease course (disease duration was 11.6 (8) years), a condition that may have had a significant impact both on the risk of cardiovascular events[34] and on the measured association between CRP, predicted 10-year risk and individual components of ERS-RA risk score.

Fourth, the definition of hypertension and diabetes based on the use of drugs that are employed also for the treatment of other conditions (heart failure and metabolic associated fatty liver disease) and the definition of hyperlipidemia using less stringent criteria than those recently endorsed by the ESC/EAS for the management of dyslipidemia[35], may have influenced the estimation of the prevalence of conventional cardiovascular risk factors in our RA cohort.

Last, CRP plasma concentrations were available in 865 out of 1.251 RA patients; however, results obtained after multiple imputation analysis were virtually identical.

CONCLUSIONS

In summary, we observed, in a large cohort of RA patients without previous cardiovascular events, a significant, positive, and independent association between CRP plasma concentrations and 10-year cardiovascular risk estimated by ERS-RA. Our findings support the concept that measures to reduce the residual inflammatory burden may limit the incidence of cardiovascular events in the RA population.

Abbreviations

ACPA, anti-citrullinated peptide antibodies; btsDMARDs, biologic and targeted synthetic disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; CORDIS, Cardiovascular Obesity and Rheumatic Disease Study; CRP, C-reactive protein; CV, cardiovascular; DAS-28, Disease activity score-28 joints; ERS-RA, Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis; HAQ, Health Assessment Questionnaire; HR, Hazard ratio; OR, Odds Ratio; RA, rheumatoid arthritis; RF; rheumatoid factor.

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None

Authors' contributions

GLE designed the study. All Authors were responsible for acquisition of data. GLE and RJW analysed the data. GLE wrote the draft. All authors were responsible for interpretation of the data and for drafting, revising and approving the final submitted manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article. Data are available upon request to qualified investigators.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the local Ethical Committee (GISEA Registry protocol, DG-624/2012) and a written informed consent was obtained from all enrolled

Consent for publication

Not applicable

Competing interests

All Authors report no conflict of interest.

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Table 1 Patients' characteristics

	Observations	Value
Age, years	1,251	60.4(9.3)
Female sex, n (%)	1,251	977 (78.1)
Disease duration, months	1,248	141(107)
Disease duration >120 months, n (%)	1,251	659 (52.6)
ACPA positivity, n (%)	1,205	784 (65.1)
RF positivity, n (%)	1,211	806 (66.5)
CRP, mg/L	866	6.8 (12.1)
CDAI	1,251	9(9.3)
HAQ	1.251	0.77(0.7)
Prednisone use, n (%)	1,251	539 (43)
csDMARDs use, n (%)	1,251	885 (70.7)
b/tsDMARDs use, n (%)	1,251	676 (54.0)
Hypertension, n (%)	1,251	668(53.4)
Smoke, n (%)	1,251	270 (21.5)
Hyperlipidemia, n (%)	1,220	746 (59.6)
Diabetes, n (%)	1,251	117 (9.35)
ERS-RA score	1,251	0.129(0.10)
ERS-RA <0.5, n (%)		289 (23.1)
ERS-RA >=0.5 <0.10, n (%)		349 (27.9)
ERS-RA >=0.10 <0.20, n (%)		370 (29.5)
ERS-RA >0.20, n (%)		243 (19.42)

Values are mean(1SD) or n (%). ACPA, anti-citrullinated peptide antibodies; RF, rheumatoid factor; CRP, C-reactive protein concentrations, mg/dL; CDAI, clinical disease activity index; HAQ, Health Assessment Questionnaire; cs DMARDs, conventional synthetic DMARDs; b/tsDMARDs, biological or targeted synthetic disease-modifying anti-rheumatic drugs; ERS-RA, Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis.

Table 2 Multiple regression

	Model 1 n= 865		Model 2 n= 1, 251	
ERS-RA score	Coefficient	95% CI, *p*	Coefficient	95% CI, *p*
CRP, every 10 mg/L increment	0.005	0.000 to 0.111, 0.047	0.006	0.000 to 0.012, 0.039
btsDMARD use	-0.002	-0.006 to 0.001, 0.160	-0.000	-0.003 to 0.002, 0.895
csDMARD use	0.002	-0.003 to 0.008, 0.422	0.002	-0.002 to 0.007, 0.371

A multiple linear regression (ENTER method) was performed for the dependent variable ERS-RA score using a listwise deletion analysis (Model 1) and a multiple imputation analysis (Model 2).

Table 3. Indirect, direct and total effects of ERS-RA components and medications on the ERS-RA score, using CRP as a mediator.

	Indirect	**p-value**	**Direct**	**p-value**	**Total**	**p-value**
Smoking	0.001(0.001)	0.343	0.813(0.814)	<0.001	0.814(0.143)	<0.001
Female sex	0.000(0.000)	0.723	0.483(0.013)	<0.001	-0.484(0.013)	<0.001
Prednisone use	0.001(0.001)	0.307	0.432(0.011)	<0.001	0.433(0.011)	<0.001
Diabetes	0.001(0.001)	0.361	0.365(0.020)	<0.001	0.366(0.020)	<0.001
Disease duration	0.000(0.000)	0.348	0.309(0.011)	<0.001	0.310(0.011)	<0.001
Hyperlipidemia	-0.001(0.001)	0.317	0.302(0.011)	<0.001	0.301(0.011)	<0.001
Hypertension	0.000(0.000)	0.379	0.188(0.012)	<0.001	0.188(0.012)	<0.001
Age	-0.000(0.000)	0.440	0.058(0.000)	<0.001	0.058(0.000)	<0.001
csDMARDs	0.000(0.000)	0.919	0.138(0.005)	0.009	0.013(0.005)	0.008
CDAI	0.000(0.000)	0.300	0.009(0.000)	<0.001	0.009(0.000)	<0.001
ln-CRP	-	-	0.006(0.005)	0.271	0.006(0.005)	0.271
b/tsDMARDs	-0.000(0.000)	0.299	0.005(0.003)	0.008	0.005(0.003)	0.102

Number are standardised effect estimates (standard error). Table shows each variable in order of the standardised total effect; Disease duration, disease duration >10 years; csDMARDs, conventional synthetic DMARDs; CDAI, Clinical Disease Activity index; b/tsDMARDs, biological or targeted synthetic DMARDs

Image 1 Ln-CRP plasma concentrations according to ERS-RA risk score categories